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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,446	08/16/2000	Fang Fang	014357/0278749	9403

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 04/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/555,446	FANG, FANG	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-10,13-16,19,20,27-29,31-33 and 35-42* is/are pending in the application.

4a) Of the above claim(s) *13-16,28,32,35 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10,19,20,27,29,31,33 and 37-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed November 24, 2004 in response to the Office Action of May 21, 2004 is acknowledged and has been entered. Claims 7-10,19,20,27,29,31,33 and 37-42 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Objections

The objection to the specification **is withdrawn** in view of applicants showing that they have submitted a prior amendment inserting the sequence identifiers.

Claim Rejections - 35 USC § 103

The rejection of claims 7-9, 19, 20, 27, 29, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Adair et al. (WO 91/16927, see IDS October 20, 2003) in view of King et al. (U.S. Pat. No. 6,307,026 B1) and Hodits et al. (Journal of Biological Chemistry, 1995) **is withdrawn** in view of applicants amendments to the claim. Specifically applicants have amended the claims to require that the antibody binding domains be polymerized through a coiled-coil sequence.

New rejection in view of applicants amendments to the claims:

Claims 7-9, 19, 20, 27, 29, 31, 33 and 37-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adair et al. (WO 91/16927, see IDS October 20, 2003), Kipriyanov et al.

(Protein Engineering, 1996), Pack et al. (Journal of Molecular Biology, 1995, see IDS February 12, 2001) and Hodits et al. (Journal of Biological Chemistry, 1995).

The instant invention is drawn to a multivalent recombinant antibody, which include any multimeric configuration of two or more recombinant antibodies. The multivalent recombinant antibody is directed to ICAM-1. The antibody is formulated for the prevention of rhinovirus infection. The formulation includes antibodies to the LDL receptor. The claims are drawn to a method of administering the antibody for the prevention of the common cold or acute otitis.

Applicants have amended the claims to change the binding affinity constant of the multivalent recombinant antibody. Applicants have also included the requirement that polymerization is achieved through the use of a coiled-coil sequence.

Applicants' arguments are (1) that none of the references individually or in combination instant teach antibodies with an apparent affinity of 10^9 M^{-1}. (2) Applicant disagrees with the conclusion of the cited reference that stronger protection is seen when the scFV7 is made bivalence through the use of an anti-myc antibody. Applicants' argument is that there is no data to support the finding of the author other than the observational note made in the reference. Applicant then puts forth other possible mechanism to explain the observation that greater protection is achieved when the scFv is incubated in the presence of an anti-c-myc antibody.

In response to applicants arguments (1) it is well established in the art that by increasing the antigen binding sites (i.e. increasing the valency of the product) in a scFV complex increases the apparent affinity of that complex. Therefore, the new limitation that the claimed compositions possess an apparent affinity of 10^9 M^{-1} falls within the realm of optimizing the

composition. (2) The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965).

Adair et al. teaches the production of a humanized CDR- grafted antibody for the binding of ICAM-1. The antibodies have the same specificity as the R6-5-D5 antibody (page 31, lines 19-25, also see claims 1, 16). The reference teaches recombinant antibodies, having two antigen binding sites (multivalent), as an anti-inflammatory agent (see pages 32-35; page 33, lines 25-33) for the treatment of viral infection, especially rhinoviral infection (see claims 36-38), or for a method of treating inflammation (see claim 30). The Office does not have laboratory facilities to test whether the antibodies of the prior art binds ICAM-1 with a specificity of 10^9 M^{-1}. Barring any evidence to the contrary the presumption is that the prior art antibodies will bind ICAM-1 epitopes with the requisite specificity.

Kipriyanov et al. teaches the production of an antibody complex that uses single chain antibody fragments that are linked to streptavidin. The tetrameric complex in the cited reference also is able to bind 3.5 molecules of biotin thereby retain full biotin binding ability. The reference teaches that by increasing the valency of the single chain antibody the binding affinity also increases (see table 2, page 209). The association rate for the scFV:streptavidin tetramer was 35 times higher than the single chain scFV fragment alone. The reference does not teach an anti ICAM-1 multivalent complex.

Pack et al. teaches that a multivalent trimeric or tetrameric single chain antibody construct is obtained by the addition of the leucine zipper dimerization domain of GCN4 (a coiled coil domain). The GCN4 zipper is fused to the single chain antibody at the hinge region. Nature teaches that polymerizing low affinity molecules increases the functional affinity of the

complex. This is observed in the decavalent IgM molecule. The reference does not teach an anti ICAM-1 multivalent complex.

Hodits et al. teaches the production of single chain fragment antibodies against the low density lipoprotein receptor (LDL). These antibodies were able to inhibit viral infection in cells (see figure 7). The protection of the antibody was increased by binding the single chain antibodies using a *myc*-sequence tag (see page 24084, last paragraph), by making the molecule multivalent.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase the affinity of an antibody complex by increasing the valency of the complex as taught by Kipriyanov et al. One having ordinary skill in the art would have been motivated to utilize the recombinant antibodies taught by Adair et al. and to increase there binding capacity by fusing a polymerization sequence to the antibody. Formulating a combination of ICAM-1 directed antibodies and LDL antibodies into a single use formulation would have been motivated by Hodits et al. which indicates that rhinoviruses gain entry into the host cell via the LDL receptor (minor group) and via the ICAM-1 (major group). A formulation containing antibodies directed to both group would provide protection against rhinovirus displaying surface molecules associated different serotypes (see Hodits et al. page 24084, column 2, 2nd paragraph). Therefore, the instant invention directed to multivalent antibodies for the protection of rhinovirus infection is obvious Adair et al. and Kipriyanov et al. and Pack et al. in view of Hodits et al.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 9/4/05